



**DRAFT MONOGRAPH FOR *THE INTERNATIONAL
PHARMACOPOEIA***

PARACETAMOL ORAL SOLUTION

(September 2010)

DRAFT FOR COMMENTS

This document was provided by a quality control expert and was discussed at the recent WHO tele-/videoconference on specifications for medicines and quality control laboratory issues held on 25 August 2010. Should you have any comments thereon, please send these to Dr S. Kopp, Manager, Medicines Quality Assurance Programme, Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland; fax: (+41 22) 791 4730 or e-mails: kopps@who.int with a copy to Dr Herbert Schmidt (schmidh@who.int) by 10 November 2010.

In order to speed up the process of receipt of comments, if you do not already receive our documents electronically, please let us have your e-mail address (to bonnyw@who.int) and we will add it to our electronic mailing list.

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SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT

QAS/10.385

International Pharmacopoeia monograph on Paracetamol oral solution

	Date
Preparation of first draft by laboratory	August 2010
Preliminary discussion of the first draft during the tele-/ videoconference on specifications for medicines and quality control laboratory issues	25 August 2010
Mailing of draft monograph for comments	September 2010
Collation of comments received	October-November 2010
Presentation to WHO Expert Committee on Specifications for Pharmaceutical Preparations	18-22 October 2010
Any further action as required	...

DRAFT PROPOSAL FOR *THE INTERNATIONAL PHARMACOPOEIA*

Paracetamol oral solution

(September 2010)

Other name. Acetaminophen oral solution.

Category. Non-opioid analgesic

Storage. Paracetamol oral solution should be kept in a well-closed container having a child-resistant closure, protected from light. The solution should not be refrigerated.

Additional information

Strength in the current WHO Model list of essential medicines: 125 mg per 5 ml (25 mg per ml). Strength in the current WHO Model list of essential medicines for children: 125 mg per 5 ml (25 mg per ml).

Requirements

Complies with the monograph for "[Liquid preparations for oral use](#)".

Definition. Paracetamol oral solution is a solution of paracetamol in a suitable flavoured vehicle. It contains not less than 90.0% and not more than 110.0% of the amount of paracetamol (C₈H₉NO₂) stated on the label.

Manufacture. The method of manufacture is validated to demonstrate that the oral solution, if tested, would comply with the following test.

Diethylene glycol and ethylene glycol

Carry out the test as described under [1.14.5 Gas chromatography](#). Use a capillary glass or quartz column (30m × 0.53 mm), the inner surface of which is coated with a thick layer of macrogol 20M R (1.0 µm). Maintain the temperature of the column at 100°C for 5 minutes. Increase the temperature at a rate of 10°C per minute to 230°C, and maintain it at this point for 4 minutes. Maintain the temperature of the injection port and the detector at 230°C. Use helium R as the carrier gas with a linear velocity of about 38 cm per second; use splitless injection followed by a split ratio of 1:20 after 30 sec; use a flame-ionization detector.

Prepare the following solutions in a 1:1 mixture of acetonitrile R and water R: for solution (A) weigh 0.350 g of 1,4-butanediol R and dilute to 100 ml; for solution (B) weigh 10.0 g of Paracetamol oral solution, add 2.0 ml of solution (A) and dilute to 100 ml; for solution (C) weigh 0.500 g of each ethylene glycol R, propylene glycol R and diethylene glycol R and dilute to 100 ml; for solution (D) mix 2.0 ml of solution (C) with 2.0 ml of solution

(A) and dilute to 100 ml; for solution (E) weigh 10.0 g of Paracetamol oral solution, add 2.0 ml of solution (A), 2.0 ml of solution (C) and dilute to 100 ml.

Inject separately 1.0 µl each of solutions (B), (D) and (E) and record the chromatograms. The relative retention times of the analytes are about 0.73 for propylene glycol, 0.76 for ethylene glycol, 1.00 for 1,4-butanediol, 1.04 for diethylene glycol, and 1.27 for glycerol.

The test is not valid unless peaks corresponding to ethylene glycol and diethylene glycol can be detected in solution (E) and the resolution between the peaks corresponding to ethylene glycol and propylene glycol in solution (D) is at least 4.0.

Measure the areas of the peak responses obtained in the chromatograms from solutions (B) and (D). The mean areas of the ethylene glycol and diethylene glycol peaks obtained with solution (B) are not greater than the mean area of the corresponding peak obtained with solution (D) (0.1% of ethylene glycol and 0.1% diethylene glycol).

Identity tests

A. Carry out test A.1 or, where UV detection is not available, test A.2.

- A.1 Carry out the test as described under [1.14.1 Thin-layer chromatography](#), using silica gel R6 as the coating substance and a mixture of 50 volumes of acetone R, 50 volumes of toluene R and 1 volume of glacial acetic acid R as the mobile phase.

Apply separately to the plate 10 µl of each of the following two solutions in methanol R. For solution (A) shake a volume of the oral solution containing 125 mg of paracetamol with 25 ml, dilute to 50 ml, filter, and use the filtrate. For solution (B) use 2.5 mg of paracetamol RS per ml. .

After removing the plate from the chromatographic chamber, allow it to dry in a current of warm air.

Examine the chromatogram in ultraviolet light (254 nm).

The principal spot obtained with solution (A) corresponds in position, appearance, and intensity to that obtained with solution (B).

- A.2 Carry out the test as described under [1.14.1 Thin-layer chromatography](#), using the conditions described above under test A.1 but using silica gel R5 as the coating substance. After removing the plate from the chromatographic chamber, allow it to dry in a current of warm air, place in chamber with iodine vapours, and allow to stand for 20 minutes. Examine the chromatogram immediately in daylight.

The principal spot obtained with solution (A) corresponds in position, appearance, and intensity to that obtained with solution (B).

- B. See the test described below under Assay. The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that obtained with solution (2).

4-Aminophenol. Prepare fresh solutions, protect solutions from light and perform the test without delay. Carry out the test as described under [1.14.4 High-performance liquid chromatography](#), using the same chromatographic conditions as described under Assay but using 272 nm as the detection wavelength.

Prepare the following solutions. For solution (1), withdraw a quantity of the oral solution containing the equivalent of 125 mg of paracetamol, and shake with about 15 ml of the solvent mixture. Dilute to 25 ml with the solvent mixture. Filter through a 0.45- μ m filter, discarding the first few ml of the filtrate. For solution (2), dissolve 12.5 mg of 4-aminophenol R in about 20 ml of solvent mixture, and dilute to 50 ml with the solvent mixture. Dilute 5 ml of this solution to 50 ml with the solvent mixture.

Inject separately 20 μ l of solutions (1) and (2) and record the chromatograms.

Depending on the formulation of the oral solution, there may be late-eluting preservatives or other excipients (e.g. potassium sorbate, sodium benzoate, vanillin and methyl hydroxybenzoate) present that can interfere with subsequent chromatographic runs.

In the chromatogram obtained with solution (1), the area of any peak corresponding to 4-aminophenol is not greater than the area of the corresponding peak in the chromatogram obtained with solution (2) (0.5%).

Assay. Carry out the test as described under [1.14.4 High-performance liquid chromatography](#), using a stainless steel column (25 cm x 4.6 mm), packed with octasilyl silica gel for chromatography (5 μ m) (A Luna C8(2) column is suitable). Prepare a solvent mixture consisting of 0.4 volumes of formic acid (~1080 g/l) TS, 15 volumes of methanol R and 85 volumes of water R. As the mobile phase use a filtered and degassed solution of 0.01M sodium butanesulfonate R in the above solvent mixture.

Operate at ambient temperature with a flow rate of 1.0 per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 243 nm.

Prepare the following solutions. For solution (1), withdraw an accurately weighed quantity of the oral solution containing the equivalent of about 25 mg of paracetamol, and shake with about 60 ml of the solvent mixture. Dilute to 100 ml with the solvent mixture. Dilute 10 ml of the resulting solution to 50 ml with the solvent mixture. Filter a portion of this solution through a 0.45- μ m filter, discarding the first few ml of the filtrate. For solution (2), accurately weigh about 12.5 mg of paracetamol RS and dissolve in about 30 ml of solvent mixture. Dilute this solution to 50 ml with the

solvent mixture. Dilute 10 ml of the resulting solution to 50 ml with the solvent mixture.

Inject separately 20 µl each of solutions (1) and (2) and record the chromatograms.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2).

Determine the weight per ml (1.3.1) of the oral solution and calculate the content of paracetamol ($C_8H_9NO_2$), weight in volume, in the oral solution.

Reagents to be added to *The International Pharmacopoeia*:

1,4 Butanediol R. Butane-1,4-diol; Tetramethylene glycol; $C_4H_{10}O_2$; Contains not less than 990g/kg of $C_4H_{10}O_2$.

Description. A colourless, viscous liquid.

Miscibility. Miscible with water and ethanol (~750g/l) TS.

Melting point. About 16-20°C.

Boiling range. About 230-235°C.

Mass density(ρ_{20}). About 1.017 kg/l.

Refractive index (n_{20}^D). About 1.446.

Ethylene glycol R. Ethane-1,2-diol; $C_2H_6O_2$. Contains not less than 990g/kg of $C_2H_6O_2$.

Description. Colourless, slightly viscous liquid, hygroscopic, miscible with water and with ethanol (~750g/l) TS.

Melting point. About -12°C.

Boiling point. About 198°C.

Mass density(ρ_{20}). About 1.11 kg/l.

Refractive index (n_{20}^D). About 1.432.

Propylene glycol R. Propane-1,2-diol; $C_3H_8O_2$. Contains not less than 990g/kg of $C_3H_8O_2$.

Description. Viscous, clear, colourless, hygroscopic liquid, miscible with water and with ethanol (~750g/l) TS.

Melting point. About -59°C.

Boiling range. About 184°C to 189°C.

Mass density(ρ_{20}). About 1.036 kg/l.

Refractive index (n_{20}^D). About 1.432
